Remarks

Claims 1-62 and 68-75 are pending. Claims 1, 56, 68 and 71 have been amended. Claims 63-67 have been canceled. New claims 74 and 75 have been added.

Claims 1, 56, 68 and 71 were amended to recite that the a capture tag is a hapten, a ligand, a ligand binding molecule, an antibody or an anti-antibody. These amendments find support at least on page 36, lines 26-32.

Support for new claim 74 can be found at least in original claim 1 on which the language of claim 74 is based. New claim 74 also recites that the capture tag is attached to the rolling circle replication primers. This finds support at least on page 12, lines 11-12.

Support for new claim 75 can be found at least in original claim 56 on which the language of claim 75 is based. New claim 75 also recites that the capture tag is attached to the cDNA. This finds support at least on page 12, lines 16-17.

Rejection Under 35 U.S.C. § 102

Claims 1-15, 18-29, 31-47, 53-58, 61, 62, 68, and 70-72 were rejected under 35 U.S.C. § 102(b) as being anticipated by Lizardi et al. (U.S. Pat. No. 6,316,229 B1). Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Lizardi et al. discloses compositions and a method for detecting single nucleic acid molecules using rolling circle amplification (RCA) of amplification target circles (ATC), primed by immobilized primers. In one form of the method, referred to as bipartite primer rolling circle amplification (BP-RCA), RCA of the ATC depends on the formation of a primer by target-mediated ligation. In BP-RCA a probe and a combination probe/primer oligonucleotide, in the presence of a nucleic acid molecule having the target sequence, can hybridize to adjacent sites on the target sequence allowing the probes to be ligated together. The ligated primer can then be used to prime replication of its cognate ATC.

The passages of Lizardi et al. cited in the Office Action fail to disclose use of a capture tag to associate cDNA with a rolling circle replication primer where the capture tag is a hapten, a ligand, a ligand binding molecule, an antibody or an anti-antibody. The passages of Lizardi et al. cited in the Office Action also fail to disclose or refer specifically to RT primers. The passages of Lizardi et al. cited in the Office Action also fail to disclose RT primers that comprise a capture

tag or use of such a capture tag to associate a rolling circle replication primer with cDNA. The passages of Lizardi et al. cited in the Office Action also fail to disclose RT primers that comprise a rolling circle replication primer portion or use of such a rolling circle replication primer portion of an RT primer to associate the rolling circle replication primer portion with an amplification target circle.

Arguments For Claims 1-15, 18-29, 31-47, 56-58, 61, 68 and 71

In the method of claims 1-15, 18-29, 31-47, 56-58, 61, 68 and 71, cDNA produced from mRNA is associated with rolling circle replication primers, where the rolling circle replication primers or the cDNA comprise capture tags, where the capture tag is a hapten, a ligand, a ligand binding molecule, an antibody or an anti-antibody, and where the association between the rolling circle replication primers and cDNA occurs via the capture tags. That is, the claims require the capture tag to be a hapten, a ligand, a ligand binding molecule, an antibody or an anti-antibody and further require the association between the rolling circle replication primers and cDNA to occur via the capture tag. See step (c) of claim 1; step (c) of claim 56, lines 6-8 of claim 68; and lines 6-8 of claim 71.

The cited passage of Lizardi et al. fails to disclose use of a capture tag to associate cDNA with a rolling circle replication primer where the capture tag is a hapten, a ligand, a ligand binding molecule, an antibody or an anti-antibody. The Office Action alleges (page 3, line 1) that Lizardi et al. teaches "mixing one or more rolling circle replication primers with the cDNA strands under conditions that promote association of the cDNA strands with the rolling circle replication primers, wherein the rolling circle replication primers each comprise a capture tag, and wherein association occurs via the capture tag." For support, the Office Action cites column 42, lines 27-52 of Lizardi et al., which describes a method of carrying out BP-RCA where RCA of the ATC depends on the formation of a primer by target mediated ligation (column 41, lines 5-8). However, the cited passage of Lizardi et al. actually describes formation of a rolling circle replication primer by target-mediated ligation of two oligonucleotides: a half probe and a probe/primer. The half probe and a portion of the probe/primer hybridize to a target DNA molecule via base pairing. Thus, association of the primer and the target DNA molecule in Lizardi et al. occurs by a nucleotide to nucleotide base pairing interaction between the sequences

of the target DNA molecule and of the half probe and probe/primer, not by interaction of, for example, a hapten or ligand.

The cited passage of Lizardi et al. fails to disclose use of a capture tag to associate cDNA with a rolling circle replication primer where the capture tag is a hapten, a ligand, a ligand binding molecule, an antibody or an anti-antibody. Because Lizardi et al. fails to disclose every feature of the claimed method, Lizardi et al. fails to anticipate claims 1-15, 18-29, 31-47, 56-58, 61, 68 and 71.

Arguments For Claims 53-55 and 70

In the method of claims 53-55 and 70, cDNA produced from mRNA is associated with rolling circle replication primers, where the RT primers used to produce the cDNA comprise capture tags, and where the association between the rolling circle replication primers and cDNA occurs via the capture tags. That is, the claims require use of an RT primer that comprises a capture tag that is the basis for the association of the rolling circle replication primers and the cDNA.

The cited passage of Lizardi et al. fails to disclose or refer specifically to RT primers, fails to disclose RT primers that comprise a capture tag, and fails to disclose use of such a capture tag to associate a rolling circle replication primer with cDNA. The Office Action alleges (page 2, lines 16-18) that Lizardi et al. teaches "mixing one or more RT primers with a nucleic acid sample and reverse transcribing to produce cDNA strands each comprising one of the RT primers, wherein each RT primer comprises a reverse transcription primer portion." For support, the Office Action cites column 77, line 2 of Lizardi et al., which merely mentions use of cDNA produced by reverse transcription. The passage does not mention any primers used to produce cDNA, does not describe any features of such primers, and does not describe the use of such primers. Thus, the cited passage of Lizardi et al. fails to disclose or refer specifically to RT primers, fails to disclose RT primers that comprise a capture tag, and fail to disclose use of such a capture tag to associate a rolling circle replication primer with cDNA. Most significantly, the Office Action fails to address the requirement of the claims that the RT primers used to produce the cDNA comprise capture tags and that the association between the rolling circle replication

primers and cDNA occurs via the capture tags. Because Lizardi et al. fails to disclose every feature of the claimed method, Lizardi et al. fails to anticipate claims 53-55 and 70.

Arguments for Claims 62 and 72

The method of claims 62 and 72 requires the use of RT primers that comprise a rolling circle replication primer portion and use of such a rolling circle replication primer portion of an RT primer to associate the rolling circle replication primer portion with an amplification target circle. That is, the claims require use of an RT primer that comprises a rolling circle replication primer portion that is the basis for the association of the rolling circle replication primers with amplification target circles.

The cited passage of Lizardi et al. fails to disclose RT primers that comprise a rolling circle replication primer portion or use of such a rolling circle replication primer portion of an RT primer to associate the rolling circle replication primer portion with an amplification target circle. The Office Action alleges (page 2, lines 16-18) that Lizardi et al. teaches "mixing one or more RT primers with a nucleic acid sample and reverse transcribing to produce cDNA strands each comprising one of the RT primers, wherein each RT primer comprises a reverse transcription primer portion." For support, the Office Action cites column 77, line 2 of Lizardi et al., which merely mentions use of cDNA produced by reverse transcription. The passage does not mention any primers used to produce cDNA, does not describe any features of such primers, and does not describe the use of such primers. Thus, the cited passage of Lizardi et al. fails to disclose or refer specifically to RT primers, fails to disclose RT primers that comprise a rolling circle replication primer portion, and fail to disclose use of such an RT primer to associate the rolling circle replication primer portion with an amplification target circle. Most significantly, the Office Action fails to address the requirement of the claims that the RT primers used to produce the cDNA comprise rolling circle replication primer portions and that the RT primers associate with amplification target circles via the rolling circle replication primer portions. Because Lizardi et al. fails to disclose every feature of the claimed method, Lizardi et al. fails to anticipate claims 62 and 72.

Additional Arguments for Claims 37-39

The method of claims 37-39 requires the use of RT primers that comprise a capture tag. The cited passage of Lizardi et al. fails to disclose RT primers that comprise a capture tag. The Office Action alleges (page 5, lines 16-19) that Lizardi et al. teaches "the RT primer comprises a capture tag" and that "the capture tag is selected from the group consisting of biotin, digoxigenin, bromodeoxyuridine, or other hapten." For support, the Office Action cites column 23, lines 50-67 of Lizardi et al., which discloses detection labels for nucleic acid amplified using rolling circle amplification and rolling circle transcription. See column 23, lines 18-23. The labels disclosed in the cited passage of Lizardi et al. are to be incorporated into or associated with amplified nucleic acids. This is not the same as what is presently claimed.

The present method uses the claimed RT primers to produce cDNA the presence of which allows production of amplified nucleic acid. In other words, neither the claimed RT primers nor the claimed cDNA produced with the RT primers are equivalent to the amplified nucleic acid referred to in column 23 of Lizardi et al. Lizardi et al. fails to disclose or refer to RT primers or cDNA and fails to disclose RT primers and cDNA that comprise the listed labels (such as biotin, digoxigenin, bromodeoxyuridine, and other haptens). Because Lizardi et al. fails to disclose every feature of the claimed method for these additional reasons, Lizardi et al. fails to anticipate claims 37-39.

Additional Arguments for Claims 39-41

The method of claims 39-41 requires the use of cDNA that comprises a capture tag. The cited passage of Lizardi et al. fails to disclose cDNA that comprises a capture tag. The Office Action alleges (page 5, lines 19-23) that Lizardi et al. teaches "the cDNA strands comprise capture tags" and that "the capture tags on the cDNA strands are selected from the group consisting of biotin, digoxigenin, bromodeoxyuridine, or other hapten." For support, the Office Action cites column 23, lines 50-67 of Lizardi et al., which discloses detection labels for nucleic acid amplified using rolling circle amplification and rolling circle transcription. See column 23, lines18-23. The labels disclosed in the cited passage of Lizardi et al. are to be incorporated into or associated with amplified nucleic acids. This is not the same as what is presently claimed.

The present method uses the presence of cDNA to enable production of amplified nucleic acid. In other words, the claimed cDNA is not equivalent to the amplified nucleic acid referred to in column 23 of Lizardi et al. Lizardi et al. fails to disclose or refer to cDNA and fails to disclose cDNA that comprises the listed labels (such as biotin, digoxigenin, bromodeoxyuridine, and other haptens). Because Lizardi et al. fails to disclose every feature of the claimed method for these additional reasons, Lizardi et al. fails to anticipate claims 39-41.

Additional Arguments for Claims 46 and 47

The method of claims 46 and 47 requires the use of cDNA that comprises a capture tag. The cited passage of Lizardi et al. fails to disclose cDNA that comprises a capture tag. The Office Action alleges (page 6, lines 3-5) that Lizardi et al. teaches "the capture tags on the cDNA strands are biotin." For support, the Office Action cites column 53, lines 53-57 of Lizardi et al., which discloses labels in tandem sequence DNA (TS-DNA; which is the product of rolling circle amplification). The labels disclosed in the cited passage of Lizardi et al. are to be incorporated into or associated with amplified nucleic acids (TS-DNA). This is not the same as what is presently claimed.

The present method uses the presence of cDNA to enable production of amplified nucleic acid. In other words, the claimed cDNA is not equivalent to the amplified nucleic acid (TS-DNA) referred to in column 53 of Lizardi et al. Lizardi et al. fails to disclose or refer to cDNA and fails to disclose cDNA that comprises labels. Because Lizardi et al. fails to disclose every feature of the claimed method for these additional reasons, Lizardi et al. fails to anticipate claims 46 and 47.

For all of the above reasons, Lizardi et al. fails to anticipate claims 1-15, 18-29, 31-47, 53-58, 61, 62, 68, and 70-72.

Rejection Under 35 U.S.C. § 103

1. Claims 16-17 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Lizardi et al. (U.S. Pat. No. 6,316,229 B1; Lizardi '229) in view of Lizardi (U.S. 2003/0032024 A1; Lizardi '024). Applicants respectfully traverse this rejection to the extent it is applied to the claims as amended.

In order for a reference or a combination of references to anticipate a claim or claims, "[f]irst, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations." MPEP § 2143.

Applicants first note that claims 16 and 17 properly depend from claim 1 and therefore, by definition, encompass all the limitations of claim 1. Secondly, Applicants note that the rejection applies Lizardi '229 in the same way and for the same disclosure for which Lizardi '229 was applied in the rejection under 35 U.S.C. § 102. For at least the reasons discussed above in connection with the rejection under 35 U.S.C. § 102, Lizardi '229 fails to disclose or suggest every limitation of claims 16 and 17. Specifically, Lizardi '229 fails to disclose or suggest use of a capture tag to associate cDNA with a rolling circle replication primer where the capture tag is a hapten, a ligand, a ligand binding molecule, an antibody or an anti-antibody.

Lizardi '024 fails to supplement the elements missing from Lizardi '229. Lizardi '024 was cited for allegedly disclosing mixing one or more half probes with the cDNA strands wherein each half probe is designed to hybridize to a cDNA strand adjacent to where a capture probe hybridizes, ligating the half probes and capture probes, and after ligation, incubating the capture probes at a temperature above the melting temperature of the capture probe but below the melting temperature of the ligated capture probe/half probe. However, Lizardi '024 fails to disclose or suggest rolling circle replication primers comprising a capture tag, where the capture tag is a hapten, a ligand, a ligand-binding molecule, an antibody or an anti-antibody, or use of a capture tag to associate cDNA with a rolling circle replication primer. Thus, Lizardi '229 and Lizardi '024, either alone or in combination, fail to disclose or suggest each and every element of claims 16 and 17. Accordingly, Lizardi '229 and Lizardi '024 do not make obvious claims 16 and 17. Applicants respectfully request withdrawal of this rejection.

2. Claim 30 was rejected under 35 U.S.C. § 103(a) as being unpatentable over Lizardi et al. (U.S. Pat. No. 6,316,229 B1) in view of Waggoner et al. (U.S. Pat. No. 6,008,373).

Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Applicants first note that claim 30 properly depends from claim 1 and therefore, by definition, encompass all the limitations of claim 1. Secondly, Applicants note that the rejection applies Lizardi et al. in the same way and for the same disclosure for which Lizardi et al. was applied in the rejection under 35 U.S.C. § 102. For at least the reasons discussed above in connection with the rejection under 35 U.S.C. § 102, Lizardi et al. fails to disclose or suggest every limitation of claim 30. Specifically. Lizardi et al. fails to disclose or suggest use of a capture tag to associate cDNA with a rolling circle replication primer where the capture tag is a hapten, a ligand, a ligand binding molecule, an antibody or an anti-antibody.

Waggoner et al. fails to supplement the elements missing from Lizardi et al. Waggoner et al. was cited for its disclosure of using phycoerythrin as a fluorophore in the detection label on an antibody. Waggoner et al. fails to disclose or suggest a rolling circle replication primer comprising a capture tag, wherein the capture tag is a hapten, a ligand, a ligand-binding molecule, an antibody or an anti-antibody or the use of a capture tag to associate cDNA with a rolling circle replication primer. Thus, Lizardi et al. and Waggoner et al., either alone or in combination, fail to disclose or suggest each and every element of claim 30. Accordingly, Lizardi et al. and Waggoner et al. do not make obvious claim 30. Applicants respectfully request withdrawal of this rejection.

3. Claims 48-52, 69 and 73 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Lizardi et al. (U.S. Pat. No. 6,316,229 B1) in view of Cao et al. (U.S. 2002/0120409). Applicants respectfully traverse this rejection.

Claims 48-52, and 69

With regard to claims 48-52, and 69 the Office Action applies Lizardi et al. in the same way and for the same disclosure for which Lizardi et al. was applied in the rejection under 35 U.S.C. § 102. Lizardi et al. discloses compositions and a method for detecting single nucleic acid molecules using rolling circle amplification (RCA) of amplification target circles (ATC), primed by immobilized primers. As noted in the Office Action (page 8, lines 16-17) Lizardi et al. fails to teach fragmenting and labeling cDNA strands to form labeled fragmented cDNA.

Applicants submit that Lizardi et al. also fails to disclose or suggest adding a capture tag to the fragmented cDNA or associating a rolling circle replication primer with fragmented cDNA via a capture tag.

The cited passages of Cao et al. describe a method of fragmenting cDNA and incorporating a label into the cDNA, where the label can be biotin. See Cao et al. claim 1 and paragraphs 0045-0049. The incorporated label then serves as a means of detecting the labeled cDNA. See Cao et al., para. 49. Cao et al. does not disclose or suggest associating rolling circle replication primers with the fragmented cDNA via the labels as is required by the present claims. Thus, the label of Cao et al. is not a capture tag as claimed.

Claims 48-52 involve a method of amplifying messenger RNA, involving fragmenting cDNA strands to form fragmented cDNA, adding a capture tag to the fragmented cDNA, mixing the fragmented cDNA with a set of capture probes under conditions that promote hybridization of the fragmented cDNA to the capture probes, mixing one or more rolling circle replication primers with the fragmented cDNA under conditions that promote association of the fragmented cDNA with the rolling circle replication primers, where the association occurs via the capture tag. Thus the claims require adding a capture tag to the fragmented cDNA where a rolling circle replication primer associates with the fragmented cDNA via the capture tag.

Claim 69 involves a method of using messenger RNA, the method comprising replicating one or more amplification target circles to produce one or more tandem sequence DNAs, wherein each tandem sequence DNA is coupled to a rolling circle replication primer, where the rolling circle replication primer is associated with a fragmented cDNA strand, where the fragmented cDNA strand is hybridized to a capture probe, where the fragmented cDNA comprises a capture tag, where the association occurs via the capture tag. Thus, like claims 48-52, the claim requires that the fragmented cDNA comprises a capture tag where the rolling circle replication primer associates with the fragmented cDNA strand via the capture tag of the cDNA strand.

Neither Lizardi et al. nor Cao et al., either alone or in combination, disclose or suggest fragmented cDNA comprising a capture tag and association of a rolling circle replication primer with the fragmented cDNA via the capture tag. Therefore, the cited publications fail to disclose

or suggest every limitation of the present claims. Accordingly, the cited publications fail to make obvious claims 48-52, and 69.

Claim 73

With regard to claim 73, Applicants first note that claim 73 does not recited fragmented cDNA so it is not clear how the present rejection relates to claim 73. The Office Action applies Lizardi et al. in the same way and for the same disclosure for which Lizardi et al. was applied in the rejection under 35 U.S.C. § 102. Lizardi et al. discloses compositions and a method for detecting single nucleic acid molecules using rolling circle amplification (RCA) of amplification target circles (ATC), primed by immobilized primers. As noted in the Office Action (page 8, lines 16-17) Lizardi et al. fails to teach fragmenting and labeling cDNA strands to form labeled fragmented cDNA. Applicants submit that Lizardi et al. also fails to disclose or suggest adding a capture tag to the fragmented cDNA, a rolling circle replication primer comprising a capture tag, or associating a rolling circle replication primer with fragmented cDNA via a capture tag.

The cited passages of Cao et al. describe a method of fragmenting cDNA and incorporating a label into the cDNA, where the label can be biotin. See Cao et al. claim 1 and paragraphs 0045-0049. The incorporated label then serves as a means of detecting the labeled cDNA. See Cao et al., para. 49. Cao et al. does not disclose or suggest associating rolling circle replication primers with the fragmented cDNA via the labels as is required by the present claims. Thus, the label of Cao et al. is not a capture tag as claimed. Cao et al. also fails to disclose or suggest a rolling circle replication primer comprising a capture tag, or associating a rolling circle replication primer with fragmented cDNA via a capture tag.

Claim 73 is a method of amplifying messenger RNA involving production of cDNA comprising capture tags, rolling circle replication primers comprising capture tags, and association of the cDNA and the rolling circle replication primers via the capture tags.

Neither Lizardi et al. nor Cao et al., either alone or in combination, discloses or suggests production of cDNA comprising capture tags, rolling circle replication primers comprising capture tags, and association of the cDNA and the rolling circle replication primers via the capture tags. First, the label of Cao et al. is not a capture tag as claimed. Second, Lizardi et al. does not disclose or suggest cDNA comprising capture tags. Third, there is no nexus between

the rolling circle amplification of Lizardi et al. and the labeled cDNA of Cao et al., let alone any suggestion to modify the method of Lizardi et al. to use the labeled cDNA of Cao et al. Thus, Lizardi et al. and Cao et al. fail to disclose or suggest every feature of claim 73 and fail to suggest combination of Lizardi et al. and Cao et al. to arrive at the claimed method. Accordingly, Lizardi et al. and Cao et al. fail to make obvious claim 73.

For at least these reasons, Lizardi et al. and Cao et al. do not make obvious claims 48-52, 69 and 73. Applicants respectfully request withdrawal of this rejection.

4. Claims 59 and 60 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Lizardi et al. (U.S. Pat. No. 6,316,229 B1) in view of Shoemaker et al. (U.S. Pat. No. 6,713,257 B2). Applicants respectfully traverse this rejection to the extent it is applied to the claims as amended.

Applicants first note that claims 59 and 60 properly depend from claim 56 and therefore, by definition, encompass all the limitations of claim 56. Secondly, Applicants note that the rejection applies Lizardi et al. in the same way and for the same disclosure for which Lizardi et al. was applied in the rejection under 35 U.S.C. § 102. For at least the reasons discussed above in connection with the rejection under 35 U.S.C. § 102, Lizardi et al. fails to disclose or suggest every limitation of claims 59 and 60. Specifically. Lizardi et al. fails to disclose or suggest use of a capture tag to associate cDNA with a rolling circle replication primer where the capture tag is a hapten, a ligand, a ligand binding molecule, an antibody or an anti-antibody.

Shoemaker et al. fails to supplement the elements missing from Lizardi et al. Shoemaker et al. was cited for its disclosure of using an amino-allyl dUTP in labeling cDNA. Shoemaker et al. fails to disclose or suggest the use of a capture tag to associate cDNA with a rolling circle replication primer. Thus, Lizardi et al. and Shoemaker et al., either alone or in combination, fail to disclose or suggest each and every element of claims 59 and 60. Accordingly, Lizardi et al. and Shoemaker et al. do not make obvious claims 59 and 60. Applicants respectfully request withdrawal of this rejection.

Pursuant to the above amendments and remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to

directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

It is believed that no fee is due with this submission. However, the Commissioner is hereby authorized to charge any fees which may be required to Deposit Account No. 14-0629.

Respectfully submitted,

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Robert A. Hodges — Date: 3/10/2005